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EXAMINER	
REDDIG, PETER J	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/520,224	MUELLER-HERMELINK ET AL.	
	Examiner	Art Unit	
	Peter J. Reddig	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *111-134* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *111-134* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/16/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The response filed on May 29, 2007 to the restriction requirement of March 27, 2007. Applicant has elected Group 23, claims 111-113 and 48 for examination. Because applicant did not distinctly and specifically point out any supposed errors in the restriction requirement, the election has been treated as an election without traverse MPEP 818.03(a).

Applicants have cancelled claims 2, 5, 7,10-14,19, 22-25,41-43, and 48, amended claims 111-113 and added new claims 114-134 asserting that the new claims read on the elected invention. This is found persuasive

2. Claims 111-134 are currently pending and under examination.

Priority

3. Acknowledgment is made of Applicants' claim for foreign priority based under 35 U.S.C. 119(a)-(d) based on German Applications filed in 102 29 906.4, 102 29 907.2, 102 30 516.1. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

It is noted that examiner has established a priority of July 2, 2003 date for the instant application, 10/520,224, because the priority of the instantly claimed invention is based on the German applications cited above, which have not been translated and the Examiner is unable to determine the information in the documents. If applicant disagrees with any rejection set forth in this action based on examiner's establishment of a priority date, July 2, 2003 for the instantly claimed application serial number 10/520,224, Applicants are invited to submit a proper translation of the priority documents and to point to page and line where support can be found establishing an earlier priority date. If Applicants choose to file a translation, then the translation

must be filed together with a statement that the translation of the certified copy is accurate, see MPEP 201.15.

Information Disclosure Statement

4. The information disclosure statement filed 3/16/2007 fails to comply with 37 CFR 1.98(a)(3) because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information, of each patent listed that is not in the English language. It has been placed in the application file, but the lined out information referred to therein has not been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 111-130 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite because they are drawn to a purified antibody or functional fragment thereof, which specifically bind a polypeptide having an approximate molecular weight of 55 or 115 kDa and it cannot be determined if the claims are drawn to detecting two fragments of a single protein or two distinct proteins that share the same epitope. Additionally, in consideration of the discrepancies often encountered in the art between protein molecular weights when determined by different methods, whenever a molecular weight is recited to characterize a protein the claim should include not only the method by which it was determined,

e.g. whether by sodium dodecyl sulfate polyacrylamide gel electrophoresis or some other method, but also whether the determination was made under denaturing or non-denaturing conditions and whether reducing or non-reducing conditions were used. Thus the metes and bounds of the claims cannot be determined.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. The specification is objected to AND claim 134 is rejected under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure, because the specification does not provide evidence that the claimed biological materials are known and readily available to the public.

Claim 134 is drawn to an antibody produced by the PM-2 cell line having DSMZ Accession No. DSM ACC2600.

Although the specification states that PM-2 cell line was deposited at the German Collection of Microorganisms and Cell Cultures on July 2, 2003 under the terms of the Budapest Treaty (see para bridging p. 21-220, it is unclear if the cell line which produces an antibody having the exact structural and chemical identity of the PM-2 monoclonal antibody are known and publicly available. Clearly, without access to the hybridoma cell lines producing said monoclonal antibodies, it would not be possible to practice the claimed invention. Therefore, suitable deposits for patent purposes are required. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to

practice the invention as claimed. Exact replication of: (1) the claimed cell line and/or (2) a cell line which produces the chemically and functionally distinct antibody claimed is an unpredictable event.

Given that the deposits were made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by Applicants, assignees or a statement by an attorney of record over his or her signature and registration number stating that the deposits have been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application **is required**. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves these specific matters to the discretion of each State.

In view of the above, it would require undue experimentation to reproduce an antibody produced by the PM-2 cell line having DSMZ Accession No. DSM ACC2600.

7. Claims 111-133 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a purified antibody or **antigen binding** fragment thereof, wherein said antibody or said **antigen binding** fragment specifically binds a polypeptide having an approximate molecular weight of 55 or 115 kDa using sodium dodecyl sulfate polyacrylamide gel electrophoresis, and wherein said polypeptide is expressed by ASPC-1 (ATCC Accession No. CRL-1682) and BXPC-3 (ATCC Accession No. CRL-1687) cells and **wherein said antibody or said antigen binding fragment comprises the sequence of SEQ ID NO:5 AND the sequence of SEQ ID NO:7**, does not reasonably provide enablement for a purified antibody or functional fragment thereof, wherein said antibody or said **functional fragment** specifically

binds a polypeptide having an approximate molecular weight of 55 or 115 kDa using sodium dodecyl sulfate polyacrylamide gel electrophoresis, and wherein said polypeptide is expressed by ASPC-1 (ATCC Accession No. CRL-1682) and BXPC-3 (ATCC Accession No. CRL-1687) cells and wherein said antibody or said functional fragment comprises a **sequence not identical to the sequence of SEQ ID NO: 5 or comprises a sequence not identical to the sequence of SEQ ID NO:7**. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are drawn to a purified antibody or functional fragment thereof, wherein said antibody or said functional fragment specifically binds a polypeptide having an approximate molecular weight of 55 or 115 kDa using sodium dodecyl sulfate polyacrylamide gel electrophoresis, and wherein said polypeptide is expressed by ASPC-1 (ATCC Accession No. CRL-1682) and BXPC-3 (ATCC Accession No. CRL-1687) cells wherein said antibody or said

functional fragment comprises a sequence of various degrees of identity to the sequence of SEQ ID NO:5 or comprises a sequence not identical to the sequence of SEQ ID NO:7.

This means that an antibody comprising only SEQ ID NO: 5 or SEQ ID NO: 7 or antibodies comprising proteins of varying degrees of identity to SEQ ID NO: 5 and/or 7 will bind the 55 or 115 kDa polypeptide expressed by ASPC-1 and BXPC-1 and also perform the other functions contemplated, such as binding to cancer cells or inhibiting cell growth.

The specification teaches that SEQ ID NO: 5 and SEQ ID NO: 7 are the amino acid sequences of the variable regions of the light and heavy chains of monoclonal antibody PM-2, see Figure 14 and 15. The specification teaches that the PM-2 monoclonal antibody expressing hybrodima cell line was generated from lymphocytes from pancreatic cancer patients fused to heteromyeloma cell lines. The specification teaches that CDRl of the PM-2 variable region light chain spans nucleotides 76-102 which encode amino acids 26-34, CDR2 spans nucleotides 154-1 74 which encode amino acids 52-58, and CDR3 spans nucleotides 289-309, which encode amino acids 97- 103. The specification teaches that CDRl of the PM-2 variable region heavy chain spans nucleotides 3 1-54 which encode amino acids 11-18, CDR2 spans nucleotides 106-129 which encode amino acids 36-43, and CDR3 spans nucleotides 244-300, which encode amino acids 82-100, see Example 2.

The specification teaches that the PM-2 antibody does not stain any normal tissue in immunohistochemical assays, while it positively stains every tumor type tested, see Example 3 and Tables 3 and 4. The specification teaches that The PM-2 antibody specifically binds to the CACO-2 human colorectal adenocarcinoma cell line (ATCC Accession No. HBT-37, DSMZ Accession No. ACC 169), the human colon carcinoma cell line COLO-320 (DSMZ Accession

No. ACC 144), the human colon carcinoma cell line COLO-206F (DSMZ Accession No. ACC 2 I), the HT-29 human colorectal adenocarcinoma cell line (ATCC Accession No. HTB-38), ASPC-1 pancreatic carcinoma cells, and BXPC-3 pancreatic carcinoma cell line, see p. 55

The specification teaches that PM-2 induces apoptosis in BXPC-3 human pancreatic carcinoma cells after 24 hours of incubation, see Example 4, and Fig. 4A and 4B, 7 and 9. Additionally, the specification teaches that PM-2 inhibits the viability and proliferation of human pancreatic carcinoma BXPC-3 cells, see Example 5 and Fig. 3 and 8.

The specification teaches that by a "functional fragment," as used herein in reference to a polypeptide, is meant a fragment that retains at least one biological activity of the full-length polypeptide. Examples of such a biological activity are the ability to specifically bind an antigen, induce apoptosis, and/or inhibit cell proliferation. These biological activities may be determined, for example, using any one of the assays described herein, see last para of p.12

The specification teaches that examples of functional fragments of an antibody are V_L, V_H, F_V, F_C, Fab, Fab', or $F(ab')_2$ fragments. The specification teaches that desirably, a "functional fragment" has an amino acid sequence that is substantially identical to a fragment, e.g., 3, 4, 5, 10, 15, 20, 15, 30, 50, 75, or 100 contiguous amino acids, of the amino acid sequence of SEQ ID NO: 5 or 7. In more desirable embodiments, a "functional fragment" is identical to a fragment of the sequence of SEQ ID NO: 5 or 7. Such a "functional fragment" may contain 3, 4, 5, 10, 15, 20, 15, 30, 50, 75, or 100 contiguous amino acids of SEQ ID NO:15 or 7, or may be the entire amino acid sequence of SEQ ID NO: 5 or 7. In desirable embodiments, such a fragment includes one or more of the Complement Determining Regions (CDR) of the V_H or the V_L regions of the PM-1, PM-2, or CM-2 antibody. For example, a functional fragment may include amino acids

26-34, 52-58, and/or 97-103 of SEQ ID NO: 5; amino acids 11-18, 36-43, and/or 82-100 of SEQ ID NO:7, see p. 13 1st para.

The specification cannot be extrapolated to the scope of the claims because it one of skill in the art could not reliably predict that the individual light or heavy chain variable chain regions of SEQ ID NO: 5 or 7 alone, antibodies or functional fragments thereof comprising sequences less than 100% identical to SEQ ID NO: 5 or SEQ ID NO: 7, or functional fragments of said antibodies would function to bind the polypeptides of approximately 55 or 115 kDA expressed by ASPC-1 and BXPC-3 cells as claimed.

In particular, it is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three complementarity determining regions (CDRs) which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin, see Janeway et al. (Immunobiology 5, 2001, p. 100-101). It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 79: 1979-1983). Rudikoff et al.

teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. Residues that are directly involved in protein functions such as binding (such as antibody CDR regions) will certainly be among the most conserved (see Bowie et al, Science, 247:1306-1310, 1990, p. 1306, col.2). The specification provides no guidance on structure or residues that are critical to the function of the invention as claimed. Although it is clear that binding specificity of the disclosed antibody is determined by the CDR regions, it is well known that this determination requires the exquisite interaction of the CDRs of both the light and heavy chains and the framework region of the antibody. In particular, although drawn specifically to humanization techniques, Gussow et al. (1991, Methods in Enzymology 203:99-121) is relevant to the instant rejection. Gussow et al. specifically teaches that the applicability of antibody humanization techniques relies on, among others, the assumption that the frameworks of the variable domains serve as a scaffold to support the CDRs in a specific way that facilitates antigen binding and further teach that it is of great importance to retain the interactions between the donor CDRs and the acceptor framework as closely as possible to the CDR-framework interactions of the original Mab. Gussow et al. further teaches that the affinity of the first fully humanized antibody CAMPATH1 was nearly 40 fold lower compared to the original rat MAb, apparently because of differences of residues in the framework region of the humanized antibody compared to those of the original antibody, particularly those located close to the CDRs. Clearly, alteration of even one amino acid residue can alter the packing of the residues within the molecule as it was demonstrated that mutation of the human Ser 27 to a Phe (the residue found in the original rat antibody at this position) restored the binding affinity of the humanized antibody close to the original affinity (see page 100).

Clearly, given the sensitivity of antibodies to even a single alteration in one CDR, one could not predict that an antibody comprising only a single defined CDR or antibody domain or a univalent fragment would function as claimed. Additionally, MacCallum et al. (J. Mol. Biol. (1996) 262, 732-745), analyzed many different antibodies for interactions with antigen and state that although CDR3 of the heavy and light chain dominate, a number of residues outside the standard CDR definitions make antigen contacts (see page 733, right col) and non-contacting residues within the CDRs coincide with residues as important in defining canonical backbone conformations (see page 735, left col.). The fact that not just one CDR is essential for antigen binding or maintaining the conformation of the antigen binding site, is underscored by Casset et al. (BBRC 2003 307:198-205), which constructed a peptide mimetic of an anti-CD4 monoclonal antibody binding site by rational design and the peptide was designed with 27 residues formed by residues from 5 CDRs (see entire document). Casset et al. also teaches that although CDR H3 is at the center of most if not all antigen interactions, clearly other CDRs play an important role in the recognition process (page 199, left col.) and this is demonstrated in this work by using all CDRs except L2 and additionally using a framework residue located just before the H3 (see page 202, left col.). Furthermore, Wu et al. (J. Mol. Biol. (1999) 294, 151-162) teach that it is difficult to predict which framework residues serve a critical role in maintaining affinity and specificity due in part to the large conformational change in antibodies that accompany antigen binding (page 152 left col.) but certain residues have been identified as important for maintaining conformation.

Although claim 120 is drawn to conservative substitutions of SEQ ID NO: 5 and 7, which increase the chance of having less effect on the activity of the protein, it is unpredictable which

amino acid at a certain position could be substituted even by conservative substitution. For example, Straub P et al, 1993, J Biol Chem 268(29): 21997-20003, teach that conservative substitutions of valine for glycine at positions 111 and 117 of cytochrome P450 2C2 result in about 50- and 7-fold reduction of activity, respectively. Kouklis PD et al, 1993, J Cell Science, 106(pt 3): 919-28, teach that a single exchange of glycine 450 of the intermediate filament protein vimentin with valine strongly interfers with the normal assembly of the intermediate filaments.

These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristics of an antibody molecule. Thus one of skill in the art would not believe it more likely than not that antibodies that comprise only SEQ ID NO: 5 or SEQ ID NO: 7 or sequences not identical to SEQ ID NO: 5 or 7 would predictably bind to the claimed proteins expressed by ASPC-1 and BXPC-3 without undue experimentation.

Furthermore, as drawn to the Fc fragment, Roitt et al. (Immunology, Third Edition (Mosby, London England) p. 1.7) teach that the Fc fragment does not comprise the antigen binding sites. Thus, one of ordinary skill in the art not believe it more likely than not that the Fc portion of an antibody would specifically bind to a given antigen without undue experimentation.

Thus, in view of the teaching in the art on it cannot be predicted the individual light or heavy chain variable chain regions of SEQ ID NO: 5 or 7 alone, antibodies or functional fragments thereof comprising sequences less than 100% identical to SEQ ID NO: 5 or SEQ ID NO: 7, or functional fragments of said antibodies would function to bind the polypeptides of approximatley 55 or 115 kDA expressed by ASPC-1 and BXPC-3. The specification provides

insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the individual light or heavy chain variable chain regions of SEQ ID NO: 5 or 7 alone, antibodies or functional fragments thereof comprising sequences less than 100% identical to SEQ ID NO: 5 or SEQ ID NO: 7, or functional fragments of said antibodies would function to bind the 55 or 115 kDa polypeptide expressed by ASPC-1 and BXPC-3, it appears that undue experimentation would be required to practice the claimed invention.

Applicant is reminded that MPEP 2164.03 teaches "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 428 F.2d 833, 166 USPQ 18, 24 (CCPA 1970) the amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly state in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order for it to be enabling. Given only lack of guidance in the specification, no one skilled in the art would accept the assertion that the claimed invention would function as contemplated or as claimed based only on the information in the specification and that known in the art at the time the invention was made.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention will function as contemplated or claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

8. If Applicants were able to overcome the rejections set forth above under 35 U.S.C. 112, first paragraph, Claim 127 would still be rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the purified antibody or functional fragment thereof of claim 111, wherein said antibody specifically binds to and inhibits proliferation of adenocarcinoma cells of the pancreas *in vitro*, does not reasonably provide enablement for the purified antibody or functional fragment thereof of claim 111, wherein said antibody specifically binds to and inhibits proliferation of other cancer cell types *in vitro* or any cancer cell *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the

amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Claim 127 is drawn to the purified antibody or functional fragment thereof of claim 111, wherein said antibody or functional fragment thereof specifically binds to and inhibits proliferation of a stomach adenocarcinoma, colorectal adenocarcinoma, squamous cell lung carcinoma, lung adenocarcinoma, squamous cell carcinoma of the esophagus, adenocarcinoma of the pancreas, urothel carcinoma of the urinary bladder, renal cell carcinoma of the kidney, adenocarcinoma of the prostate, ductal carcinoma of the breast, lobular carcinoma of the breast, adenocarcinoma of the ovary, adenocarcinoma of the endometrium, or adenocarcinoma of the uterus cell.

This means that the antibody of claim 111 can bind to and inhibit proliferation of any of the claimed carcinoma cells *in vitro or in vivo.*

The specification teaches as set forth above.

The specification teaches that the invention is related to the field of cancer treatment, see 1st para. pg. 1. The specification teaches a prophetic example of treating breast cancer with the antibodies of the invention, see Example 7.

One of skill in the are cannot extrapolate the teachings of the specification to the scope of the claim because 1) no nexus has been established between inhibiting the proliferation of all the claimed cancer cell types and because the heterogeneity of cancers is well known in the art and 2) no nexus has been established for the treatment of any cancer cell *in vivo* because the

artifactual nature of cultured cells is well known in the art and the unpredictability of developing novel cancer therapeutics is also well known in the art.

1) In particular, as drawn to cancer heterogeneity, cancers comprise a broad group of malignant neoplasms divided into two categories, carcinoma and sarcoma. The carcinomas originate in epithelial tissues while sarcomas develop from connective tissues, see Taber's Cyclopedic Medical Dictionary (1985, F.A. Davis Company, Philadelphia, p. 274). Given that not all cancers originate from the same tissue types, it is expected and known that cancers originate from different tissue types have different structures as well as etiologies and would present differently. Thus, it would not be predictably expected that a nexus, for example drawn to a connection between PM-2 and inhibition of pancreatic cell growth, would be established between two cancer types that arose from different tissue types. Further, it is well known that even two carcinomas that present on the same organ have significant differences in etiology and genetic constitution. For example, Busken, C et al, (Digestive Disease Week Abstracts and Itinerary Planner, 2003, abstract No: 850), teach that there is a difference in COX-2 expression with respect to intensity, homogeneity, localization and prognostic significance between adenocarcinoma of the cardia and distal esophagus, suggesting that these two cancers have different etiology and genetic constitution (last five lines of the abstract). Additionally, Kaiser (Science, 2006, 313, 1370) teaches that in a genomic analysis of mutations in breast and colon cancers, it was found that the cancer genes differ between each colon and breast cancers and each tumor had a different pattern of mutations. Kaiser teaches that the steps to cancer may be more complex than had been anticipated, see 3rd col. Furthermore Krontiris and Capizzi (Internal Medicine, 4th Edition, Editor-in-chief Jay Stein, Elsevier Science, 1994 Chapters 71-72, pages

699-729) teach that the various types of cancers have different causative agents, involve different cellular mechanisms, and, consequently, differ in treatment protocols. Chemotherapeutic agents are frequently useful against a specific type of neoplasm and especially with the unpredictability of the art there are no drugs broadly effective against all forms of cancer, see Carter, S. K. et al. Chemotherapy of Cancer; Second edition; John Wiley & Sons : New York, 1981; appendix C. Given the above, it is clear that it is not possible to predictably extrapolate a correlation between PM-2 and inhibition of cell growth in any tumor cell type, other than pancreatic cancer cells, based on the information in the specification and known in the art without undue experimentation.

2) As drawn to the artifactual nature of cell lines, it is well known in the art that the characteristics of cultured cell lines generally differ significantly from the characteristics of the primary tumor as set forth above. As discussed in Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p. 4), it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation in vivo. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, a petri dish cancer is a poor representation of malignancy, with characteristics profoundly

different from the human disease. Dermer further teaches that when a normal or malignant cell adapts to immortal life in culture, it takes an evolutionary-type step that enables the new line to thrive in its artificial environment and thus transforms a cell from one that is stable and differentiated to one that is not. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions. Further, the art recognizes the problem of molecular artifacts associated with cell culture. For example, Drexler et al (Leukemia and Lymphoma, 1993, 9:1-25) specifically teach, in the study of Hodgkin and Reed-Sternberg cancer cells in culture, that the acquisition or loss of certain properties during adaptation to culture systems cannot be excluded. This is exemplified by the teachings of Zellner et al (Clin. Can. Res., 1998, 4:1797-17802) who specifically teach that products are overexpressed in glioblastoma (GBM)-derived cell lines which are not overexpressed *in vivo*. Drexler et al further teach that only a few cell lines containing cells that resemble the *in-vivo* cancer cells have been established and even for the *bona fide* cancer cell lines it is difficult to prove that the immortalized cells originated from a specific cancer cell (see attached abstract). Further, Embleton et al (Immunol Ser, 1984, 23:181-207) specifically teaches that in procedures for the diagnosis of osteogenic sarcoma, caution must be used when interpreting results obtained with monoclonal antibodies that had been raised to cultured cell lines and specifically teach that cultured tumor cells may not be antigenically typical of the tumor cell population from which they were derived and it is well established that new artifactual antigens can occur as a result of

culture (see attached abstract). More recently, Zips et al (In vivo, 2005, 19:1-8) specifically teaches that despite their importance for drug testing, *in vitro* methods are beset by pitfalls and inherent limitations (p. 3, col 1). In particular the authors state that "It is obvious that cells in culture represent an artificial and simplified system. Unlike the situation *in vitro,* a tumor is a 3-dimensional complex consisting of interacting malignant and non-malignant cells. Vascularisation, perfusion and thereby, drug access to the tumor cells are not evenly distributed and in this fact consists an important source of heterogeneity in tumor response to drugs that does not exist *in vitro.* Therefore, prediction of drug effects in cancer patients based solely on *in vitro* data is not reliable and further evaluations in animal tumor systems is essential" (p. 3, col 2).

Thus, based on the cell culture data presented in the specification, in the absence of data on the effect of PM-2 antibodies on tumors *in vivo*, no one of skill in the art would not believe it more likely than not that the claimed invention would function as contemplated and claimed, that is inhibiting the proliferation of cancers *in vivo*, based only on the cell culture data provided. Further, it is well known that the art of anticancer drug discovery for cancer therapy is highly unpredictable, for example, Gura (Science, 1997, 278:1041-1042, IDS) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para). Furthermore, Kaiser (Science, 2006, 313, 1370) teaches that 90% of tumor drugs fail in patients, see 3rd col., 2nd to last para. Additionally, Young et al. (US Patent Application Pub.

20040180002, September 15, 2004) teach that there have been many clinical trials of monoclonal antibodies for solid tumors. In the 1980s there were at least 4 clinical trials for human breast cancer which produced only 1 responder from at least 47 patients using antibodies against specific antigens or based on tissue selectivity. Young et al. teach that It was not until 1998 that there was a successful clinical trial using a humanized anti-her 2 antibody in combination with cisplatin (para 0010 of the published application). The same was true in clinical trials investigating colorectal cancer with antibodies against glycoprotein and glycolipid targets, wherein the specification specifically teaches that "to date there has not been an antibody that has been effective for colorectal cancer. Likewise there have been equally poor results for lung, brain, ovarian, pancreatic, prostate and stomach cancers" (para 0011 of the published application). Thus, it is clear that the art and the specification recognize that it could not be predicted, nor would it be expected that based only on the *in vitro* data presented in the specification that it would be more likely than not that the claimed antibody or variations of the antibody claimed could be effectively used for the treatment of any cancer.

Because of the known unpredictability of the art, in the absence of *in vivo* experimental evidence, no one skilled in the art would accept the assertion that the claimed antibody is an anti-cancer antibody useful for cancer treatment or therapy. Further, the refractory nature of cancer to drugs is well known in the art. Jain (Sci. Am., 1994, 271:58-65) teaches that tumors resist penetration by drugs (p.58, col 1) and that scientists need to put expanded effort into uncovering the reasons why therapeutic agents that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of common solid tumors (p. 65, col 3). Curti (Crit. Rev. in Oncology/Hematology, 1993, 14:29-39) teaches that solid tumors resist destruction by

chemotherapy agents and that although strategies to overcome defense mechanisms of neoplastic cells have been developed and tested in a number of patients, success has been limited and further teaches that it is certainly possible that cancer cells possess many as yet undefined additional molecular mechanisms to defeat chemotherapy treatment strategies and if this is true, designing effective chemotherapeutic regimens for solid tumors may prove a daunting task (para bridging pages 29-30) and concludes that knowledge about the physical barriers to drug delivery in tumors is a work in progress (p. 36, col 2). It is clear that based on the state of the art, in the absence of *in vivo* experimental evidence, no one skilled in the art would accept the assertion that the claimed purified antibody would function as an anticancer antibody. In addition, anti-tumor antibodies must accomplish several tasks to be effective. They must be delivered into the circulation that supplies the cancer and interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. Also, the target cell must not have an alternate means of survival despite action at the proper site for the antibody. In addition variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy. The antibody may be inactivated *in vivo* before producing a sufficient effect, for example, by degradation, immunological activation or due to an inherently short half-life of the antibody. In addition, the antibody may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells and tissues where it has no effect, circulation into the target area may be insufficient to carry the antibody and a large enough local concentration may not be established. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has

been provided which would allow one of skill in the art to use the claimed invention with a reasonable expectation of success. In view of the above, one of skill in the art would be forced into undue experimentation to use the claimed invention.

Applicant is reminded that MPEP 2164.03 teaches "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the stare of the art as well as the predictability of the art. In re Fisher, 428 F.2d 833, 166 USPQ 18, 24 (CCPA 1970) the amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly state in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order for it to be enabling. Given only lack of guidance in the specification, no one skilled in the art would accept the assertion that the claimed invention would function as contemplated or as claimed based only on the information in the specification and that known in the art at the time the invention was made. For the above reasons, it appear that undue experimentation would be required to practice the claimed invention.

9. Claims 111-130 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The claims are drawn to a purified antibody or functional fragment thereof, wherein said antibody or said functional fragment specifically binds a polypeptide having an approximate molecular weight of 55 or 115 kDa using sodium dodecyl sulfate polyacrylamide gel electrophoresis, and wherein said polypeptide is expressed by ASPC-1 (ATCC Accession No. CRL-1682) and BXPC-3 (ATCC Accession No. CRL-1687) cells and wherein said antibody or said functional fragment comprises a sequence not identical to the sequence of SEQ ID NO: 5 or comprises a sequence not identical to the sequence of SEQ ID NO: 7.

The state of the art is such that it is well know in the art that determination of molecular weight by sodium dodecyl sulfate polyacrylamide gel electrophoresis is only an estimate and is unpredictably variable. In particular Sambrook et al. (Molecular Cloning, 2nd edition, Cold Spring Harbor Press, 1989, p. 18.47) teach that the determination of molecular weight by SDS-polyacrylamide gel electrophoresis is only an estimate and modifications of the polypeptide backbone, such as by glycosylation, can have a significant impact on the apparent molecular weight, see p. 18.47, 1st para.

Given the above, it is clear that in the protein biochemistry/molecular biology arts that an adequate written description is essential for one of skill in the art to recognize the antigen to which the claimed antibody binds.

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a]

written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial

structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here.

Thus, the instant specification may provide an adequate written description of a polypeptide having an approximate molecular weight of 55 or 115 kDa using sodium dodecyl sulfate polyacrylamide gel electrophoresis, and wherein said polypeptide is expressed by ASPC-1 (ATCC Accession No. CRL-1682) and BXPC-3 (ATCC Accession No. CRL-1687) that is specifically bound by the claimed antibody, per Lilly by structurally describing a representative number of polypeptides having an approximate molecular weight of 55 or 115 kDa using sodium dodecyl sulfate polyacrylamide gel electrophoresis, and wherein said polypeptide is expressed by ASPC-1 (ATCC Accession No. CRL-1682) and BXPC-3 (ATCC Accession No. CRL-1687), or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not describe a polypeptide having an approximate molecular weight of 55 or 115 kDa using sodium dodecyl sulfate polyacrylamide gel electrophoresis, and wherein said polypeptide is expressed by ASPC-1 (ATCC Accession No.

CRL-1682) and BXPC-3 (ATCC Accession No. CRL-1687) that is specifically bound by the claimed antibody, in a manner that satisfies either the Lilly or Enzo standards. The specification does not provide the complete structure of a polypeptide having an approximate molecular weight of 55 or 115 kDa using sodium dodecyl sulfate polyacrylamide gel electrophoresis, and wherein said polypeptide is expressed by ASPC-1 (ATCC Accession No. CRL-1682) and BXPC-3 (ATCC Accession No. CRL-1687) that is specifically bound by the claimed antibody, nor does the specification provide any partial structure of such a polypeptide, nor any physical or chemical characteristics of a polypeptide having an approximate molecular weight of 55 or 115 kDa using sodium dodecyl sulfate polyacrylamide gel electrophoresis, and wherein said polypeptide is expressed by ASPC-1 (ATCC Accession No. CRL-1682) and BXPC-3 (ATCC Accession No. CRL-1687) that is specifically bound by the claimed antibody, nor any functional characteristics coupled with a known or disclosed correlation between structure and function. Although the specification discloses 55 and 115 kDa polypeptides that are bound by PM-2 (see figure 5B), this does not provide a description of a polypeptide having an approximate molecular weight of 55 or 115 kDa using sodium dodecyl sulfate polyacrylamide gel electrophoresis, and wherein said polypeptide is expressed by ASPC-1 (ATCC Accession No. CRL-1682) and BXPC-3 (ATCC Accession No. CRL-1687) that is specifically bound by the claimed antibody that would satisfy the standard set out in Enzo.

The specification also fails to a polypeptide having an approximate molecular weight of 55 or 115 kDa using sodium dodecyl sulfate polyacrylamide gel electrophoresis, and wherein said polypeptide is expressed by ASPC-1 (ATCC Accession No. CRL-1682) and BXPC-3 (ATCC Accession No. CRL-1687) that is specifically bound by the claimed antibody by the test

set out in Lilly. The specification describes only 55 and 115 kDa polypeptides that are bound by PM-2 (see figure 5B). Therefore, it necessarily fails to describe a "representative number" of polypeptides having an approximate molecular weight of 55 or 115 kDa using sodium dodecyl sulfate polyacrylamide gel electrophoresis, and wherein said polypeptide is expressed by ASPC-1 (ATCC Accession No. CRL-1682) and BXPC-3 (ATCC Accession No. CRL-1687) that are specifically bound by the claimed antibody. In addition, the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

Thus, the specification does not provide an adequate written description of a polypeptide having an approximate molecular weight of 55 or 115 kDa using sodium dodecyl sulfate polyacrylamide gel electrophoresis, and wherein said polypeptide is expressed by ASPC-1 (ATCC Accession No. CRL-1682) and BXPC-3 (ATCC Accession No. CRL-1687) that is specifically bound by the claimed antibody that is required to practice the claimed invention.

11. Claims 111-133 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The claims are drawn to a purified antibody or functional fragment thereof, wherein said antibody or said functional fragment specifically binds a polypeptide having an approximate molecular weight of 55 or 115 kDa using sodium dodecyl sulfate polyacrylamide gel electrophoresis, and wherein said polypeptide is expressed by ASPC-1 (ATCC Accession No.

CRL-1682) and BXPC-3 (ATCC Accession No. CRL-1687) cells and wherein said antibody or said functional fragment comprises a sequence not identical to the sequence of SEQ ID NO: 5 or comprises a sequence not identical to the sequence of SEQ ID NO: 7.

The state of the art is such that it is well know in the art that protein biochemistry is unpredictable and that protein binding interactions, such as antibody/antigen interactions, are sensitive to even minor changes in protein sequence, thus the ability of variant antibodies to bind variant proteins is not predictable.

In particular, protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, Bowie et al (Science, 1990, 257:1306-1310,) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid alterations are possible in any given protein, the position within the protein's sequence where such amino acid alterations can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative alterations or no alterations. The exquisite sensitivity of binding proteins to alterations of even a single amino acid is well known in the art. For example, Rudikoff et al, (PNAS, USA, 1982, 79: 1979) specifically teach that even minor changes in the amino acid sequence of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function. In particular, Rudikoff et al teach that alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein results in the loss of

antigen-binding function. Additionally, MacCallum et al. (J. Mol. Biol. (1996) 262, 732-745), analyzed many different antibodies for interactions with antigen and state that although CDR3 of the heavy and light chain dominate, a number of residues outside the standard CDR definitions make antigen contacts (see page 733, right col) and non-contacting residues within the CDRs coincide with residues as important in defining canonical backbone conformations (see page 735, left col.). Furthermore, Wu et al. (J. Mol. Biol. (1999) 294, 151-162). teach that it is difficult to predict which framework residues serve a critical role in maintaining affinity and specificity due in part to the large conformational change in antibodies that accompany antigen binding (page 152 left col.) but certain residues have been identified as important for maintaining conformation. Coleman et al. (Research in Immunology, 1994; 145(1): 33-36) teach single amino acid changes in an antigen can effectively abolish antibody antigen binding. Further, the sensitivity of binding proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein.

These references demonstrate that even a single amino acid alteration or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristics of a binding protein/antigen-antibody interaction.

Furthermore, the specification teaches that examples of functional fragments of an antibody are V_L, V_H, F_V, F_C, Fab, Fab', or $F(ab')_2$ fragments. The specification teaches that desirably, a "functional fragment" has an amino acid sequence that is substantially identical to a fragment, e.g., 3, 4, 5, 10, 15, 20, 15, 30, 50, 75, or 100 contiguous amino acids, of the amino

acid sequence of SEQ ID NO: 5 or 7. In more desirable embodiments, a "functional fragment" is identical to a fragment of the sequence of SEQ ID NO: 5 or 7. Such a "functional fragment" may contain 3, 4, 5, 10, 15, 20, 15, 30, 50, 75, or 100 contiguous amino acids of SEQ ID NO: 5 or 7, or may be the entire amino acid sequence of SEQ ID NO: 5 or 7. In desirable embodiments, such a fragment includes one or more of the Complement Determining Regions (CDR) of the V_H or the V_L regions of the PM-1, PM-2, or CM-2 antibody. For example, a functional fragment may include amino acids 26-34, 52-58, and/or 97-103 of SEQ ID NO: 5; amino acids 11-18, 36-43, and/or 82-100 of SEQ ID NO:7, see p. 13 1st para

Thus, given the above, it is clear that in the antibody arts an adequate written description is essential for one of skill in the art to make and use the claimed invention which comprises numerous antibody derivatives that are required to specifically bind to the polypeptide of claim 111 as contemplated and claimed.

Given the broadly defined antibody of claim 111 and given the broad definition of the functional fragments of antibodies comprising SEQ ID NO: 5 and/or SEQ ID NO: 7, it is evident that the specification does not provide a written description of the broadly claimed antibody that is useful for a method for the prophylaxis and/or treatment of breast, lung and/or pancreatic cancer for the reasons set forth below.

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a]

written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ...i.e., complete or partial

structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. Thus, the instant specification may provide an adequate written description of the broadly claimed antibody or functional fragments thereof that specifically binds the broadly claimed polypeptide having an approximate molecular weight of 55 or 115 kDa using sodium dodecyl sulfate polyacrylamide gel electrophoresis, and wherein said polypeptide is expressed by ASPC-1 (ATCC Accession No. CRL-1682) and BXPC-3 (ATCC Accession No. CRL-1687), per Lilly by structurally describing a representative number of antibodies or functional fragments thereof that specifically bind the broadly claimed polypeptide having an approximate molecular weight of 55 or 115 kDa using sodium dodecyl sulfate polyacrylamide gel electrophoresis, or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not describe the broadly claimed antibody or functional fragments thereof that specifically binds a polypeptide having an approximate molecular weight of 55 or 115 kDa using sodium dodecyl sulfate polyacrylamide gel

electrophoresis, and wherein said polypeptide is expressed by ASPC-1 (ATCC Accession No. CRL-1682) and BXPC-3 (ATCC Accession No. CRL-1687), in a manner that satisfies either the Lilly or Enzo standards. The specification does not provide the complete structure of the broadly claimed antibody or functional fragments thereof that specifically binds a polypeptide having an approximate molecular weight of 55 or 115 kDa using sodium dodecyl sulfate polyacrylamide gel electrophoresis, and wherein said polypeptide is expressed by ASPC-1 (ATCC Accession No. CRL-1682) and BXPC-3 (ATCC Accession No. CRL-1687), nor does the specification provide any partial structure of such an antibody or functional fragments thereof, nor any physical or chemical characteristics of the broadly claimed antibody or functional fragments thereof that specifically binds a polypeptide having an approximate molecular weight of 55 or 115 kDa using sodium dodecyl sulfate polyacrylamide gel electrophoresis, and wherein said polypeptide is expressed by ASPC-1 (ATCC Accession No. CRL-1682) and BXPC-3 (ATCC Accession No. CRL-1687), nor any functional characteristics coupled with a known or disclosed correlation between structure and function. Although the specification discloses PM-2, this does not provide a description of the broadly claimed antibody or functional fragments thereof that specifically binds a polypeptide having an approximate molecular weight of 55 or 115 kDa using sodium dodecyl sulfate polyacrylamide gel electrophoresis, and wherein said polypeptide is expressed by ASPC-1 (ATCC Accession No. CRL-1682) and BXPC-3 (ATCC Accession No. CRL-1687) that would satisfy the standard set out in Enzo.

The specification also fails to describe the broadly claimed antibody or functional fragments thereof that specifically binds a polypeptide having an approximate molecular weight of 55 or 115 kDa using sodium dodecyl sulfate polyacrylamide gel electrophoresis, and wherein

said polypeptide is expressed by ASPC-1 (ATCC Accession No. CRL-1682) and BXPC-3 (ATCC Accession No. CRL-1687) by the test set out in Lilly. The specification describes only PM-2. Therefore, it necessarily fails to describe a "representative number" of species of the broadly claimed antibody or functional fragments thereof that specifically binds a polypeptide having an approximate molecular weight of 55 or 115 kDa using sodium dodecyl sulfate polyacrylamide gel electrophoresis, and wherein said polypeptide is expressed by ASPC-1 (ATCC Accession No. CRL-1682) and BXPC-3 (ATCC Accession No. CRL-1687). In addition, the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

Thus, the specification does not provide an adequate written description the broadly claimed antibody or functional fragments thereof that specifically binds a having an approximate molecular weight of 55 or 115 kDa using sodium dodecyl sulfate polyacrylamide gel electrophoresis, and wherein said polypeptide is expressed by ASPC-1 (ATCC Accession No. CRL-1682) and BXPC-3 (ATCC Accession No. CRL-1687).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

12. Claims 111-123 and 126-134 are rejected under 35 U.S.C. 102(a) as being anticipated by Brändlein et al. (Human Antibodies, 18 April 2003, 11:107-119, IDS).

The claims are drawn to:

111. A purified antibody or functional fragment thereof, wherein said antibody or said functional fragment specifically binds a polypeptide having an approximate molecular weight of 55 or 115

kDa using sodium dodecyl sulfate polyacrylamide gel electrophoresis, and wherein said polypeptide is expressed by ASPC-1 (ATCC Accession No. CRL-1682) and BXPC-3 (ATCC Accession No. CRL- 1687) cells and wherein said antibody or said functional frazment comprises a sequence at least 80% identical to the sequence of SEQ ID NO:5 or comprises a sequence at least 80% identical to the sequence of SEQ ID NO:7.

112. The purified antibody or functional fragment thereof of claim 111, wherein said antibody or said functional fragment comprises a sequence at least 85% identical to the sequence of SEQ ID NO:5 or comprises a sequence at least 85% identical to the sequence of SEQ ID NO:7.

113. The purified antibody or functional fragment thereof of claim 111, wherein said antibody or said functional fragment comprises a sequence at least 90% identical to the sequence of SEQ ID NO:5 or
comprises a sequence at least 90% identical to the sequence of SEQ ID NO:7.

114. The purified antibody or functional fragment thereof of claim 111, wherein said antibody or said functional fragment comprises a sequence at least 95% identical to the sequence of SEQ ID NO:5 or comprises a sequence at least 95% identical to the sequence of SEQ ID NO:7.

115. The purified antibody or functional fragment thereof of claim 111,
wherein said antibody or functional fragment thereof is at least 98% identical to the full length of sequence SEQ ID NO:5 or SEQ ID NO:7.

116. The purified antibody or functional fragment thereof of claim 111,
wherein said antibody or said functional fragment comprises a sequence at least 80% identical to 90 contiguous amino acids of SEQ ID NO:5 or comprises a sequence at least 80% identical to 90 contiguous amino acids of SEQ ID NO:7.

117. The purified antibody or functional fragment thereof of claim 111,
wherein said antibody or said functional fragment comprises a sequence at least 85% identical to 90 contiguous amino acids of SEQ ID NO:5 or comprises a sequence at least 85% identical to 90 contiguous amino acids of SEQ ID NO:7.

118. The purified antibody or functional fragment thereof of claim 111,
wherein said antibody or said functional fragment comprises a sequence at least 90% identical to 90 contiguous amino acids of SEQ ID NO:5 or comprises a sequence at least 90% identical to 90 contiguous amino acids of SEQ ID NO:7.

119. The purified antibody or functional fragment thereof of claim 111,
wherein said antibody or said functional fragment comprises a sequence at least 95% identical to 90 contiguous amino acids of SEQ ID NO:5 or comprises a sequence at least 95% identical to 90 contiguous amino acids of SEQ ID NO:7.

120. The purified antibody or functional fragment thereof of claim 111, wherein said antibody or said functional fragment comprises SEQ ID NO:5 and SEQ ID NO:7 with a conservative amino acid substitution in either SEQ ID NO:5 or SEQ ID NO:7.

121. The purified antibody or functional fragment thereof of claim 111, wherein said antibody or functional fragment thereof includes amino acids 26-34, 52-58 or 97-103 of SEQ ID NO:5, or includes amino acids 11-18, 36-43, or 82-100 of SEQ ID NO:7.

122. The purified antibody or functional fragment thereof of claim 111, wherein said functional fragment comprises a fragment that includes amino acids 26-34, 52- 58 and 97-103 ofSEQ ID NO:5, or that includes amino acids 11-18, 36-43, and 82-100 of SEQ ID NO:7.

123. The purified antibody or functional fragment thereof of claim 111, wherein said antibody or functional fragment thereof comprises the amino acid sequence of SEQ ID NO:5 or SEQ ID NO:7.

126. The purified antibody or functional fragment thereof of claim 111, wherein said.antibody or functional fragment thereof specifically binds to a stomach adenocarcinoma, colorectal adenocarcinoma, squamous cell lung carcinoma, lung adenocarcinoma, squamous cell carcinoma of the esophagus, adenocarcinoma of the pancreas, urothel carcinoma of the urinary bladder, renal cell carcinoma of the kidney, adenocarcinoma of the prostate, ductal carcinoma of the breast, lobular carcinoma of the breast, adenocarcinoma of the ovary, adenocarcinoma of the endometrium, or adenocarcinoma of the uterus cell.

127. The purified antibody or functional fragment thereof of claim 111, wherein said antibody or functional fragment thereof specifically binds to and inhibits proliferation of a stomach adenocarcinoma, colorectal adenocarcinoma, squamous cell lung carcinoma, lung adenocarcinoma, squamous cell carcinoma of the esophagus, adenocarcinoma of the pancreas, urothel carcinoma of the urinary bladder, renal cell carcinoma of the kidney, adenocarcinoma of the prostate, ductal carcinoma of the breast, lobular carcinoma of the breast, adenocarcinoma of the ovary, adenocarcinoma of the endometrium, or adenocarcinoma of the uterus cell.

128. The purified antibody or functional fragment thereof of claim 111, wherein said antibody or functional fragment thereof inhibits proliferation of BXPC-3 (ATCC Accession No. CRL-1687) cells.

129. The purified antibody or functional fragment thereof of claim 111, wherein said antibody or functional fragment thereof induces apoptosis of BXPC-3 (ATCC Accession No. CRL-1687) cells.

130. The purified antibody or functional fragment thereof of claim 111, wherein said antibody or functional fragment thereof specifically binds to CACO-2 cell line (ATCC Accession No. HBT-37), COLO-320 cell line (DSMZ Accession No. ACC 144), or COLO-206F cell line (DSMZ Accession No. ACC 21).

131. A purified antibody or functional fragment thereof, comprising the amino acid sequence of SEQ ID NO:5.

132. A purified antibody or functional fragment thereof, comprising the amino acid sequence of SEQ ID NO:7.

133. A purified antibody or functional fragment thereof, comprising the amino acid sequence of SEQ ID NO:5 and SEQ ID NO:7.

134. An antibody produced by the PM-2 cell line having DSMZ Accession No. DSM ACC2600.

It is noted that the specification teaches that by "purified" or "isolated" is meant separated from other components that naturally accompany it. A substantially pure factor may be obtained by chemical synthesis, separation of the factor from natural sources, or production of the factor in a recombinant host cell that does not naturally produce the factor, see p. 17, lines 20-29. Thus it is assumed for examination purposes that monoclonal antibodies produced by hybridomas in cell culture are purified antibodies.

Brändlein et al. teach PM-2 IgM monoclonal antibodies produced from lymphocytes of pancreatic carcinoma patients, see Table 1, Abstract, and Materials and Methods. Brändlein et al. teach that the PM-2 monoclonal antibody is produced by hybridomas that were generated by fusing the cells from lymph nodes or spleens of pancreatic carcinoma patients with heteromyeloma cells, see para bridgining p. 109-110. Brändlein et al. teach that the PM-2 antibody can inhibit the growth of BXPC-3 cells in vitro and induces apoptosis of BXPC-3 prostate cancer cells in vitro, see Figs. 4 and 5. Brändlein et al. teach that the PM-2 cell binds to proteins of molecular weight of approximately 55 and 115 kDa from BXPC-3 cells, see Fig. 6. Brändlein et al. teaches that PM-2 binds stomach adenocarcinoma, colorectal adenocarcinoma, squamous cell lung carcinoma, lung adenocarcinoma, squamous cell carcinoma of the esophagus, adenocarcinoma of the pancreas, urothel carcinoma of the urinary bladder, renal cell carcinoma of the kidney, adenocarcinoma of the prostate, ductal carcinoma of the breast, lobular carcinoma of the breast, adenocarcinoma of the ovary, and adenocarcinoma of the uterus tissue, see Table 4.

Given that Brändlein et al. is co-authored by the inventors of the instant invention and the PM-2 antibody was produced by the same method as that of the instant invention and exhibits the same properties as the antibody of the instant invention, the product of the prior art comprises the same product as claimed in the instant invention, that is a purified antibody or functional fragment thereof, wherein said antibody or said functional fragment specifically binds a polypeptide having an approximate molecular weight of 55 or 115 kDa using sodium dodecyl sulfate polyacrylamide gel electrophoresis, and wherein said polypeptide is expressed by ASPC-1 (ATCC Accession No. CRL-1682) and BXPC-3 (ATCC Accession No. CRL- 1687) cells and wherein said antibody or said functional frazment comprises a sequence at least 80% identical to the sequence of SEQ ID NO:5 or comprises a sequence at least 80% identical to the sequence of SEQ ID NO:7, thus the claimed product is anticipated because the product will inherently be a purified antibody or functional fragment thereof, wherein said antibody or said functional fragment specifically binds a polypeptide having an approximate molecular weight of 55 or 115 kDa using sodium dodecyl sulfate polyacrylamide gel electrophoresis, and wherein said polypeptide is expressed by ASPC-1 (ATCC Accession No. CRL-1682) and BXPC-3 (ATCC Accession No. CRL- 1687) cells and wherein said antibody or said functional frazment comprises a sequence at least 80% identical to the sequence of SEQ ID NO:5 or comprises a sequence at least 80% identical to the sequence of SEQ ID NO:7. See Ex parte Novitski 26 USPQ 1389 (BPAI 1993). Although the reference does not specifically state that the antibodies comprise SEQ ID NO: 5 and/or 7, the claimed product appears to be the same as the prior art product, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior

art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA).

Furthermore, given that Brändlein et al. is co-authored by the inventors of the instant invention and the PM-2 antibody was produced by the same method as that of the instant invention and exhibits the same properties as the antibody of the instant invention, the product of the prior art comprises the same product as claimed in the instant invention, that is an antibody produced by the PM-2 cell line having DSMZ Accession No. DSM ACC2600, thus the claimed product is anticipated because the product will inherently be an antibody produced by the PM-2 cell line having DSMZ Accession No. DSM ACC2600. See Ex parte Novitski 26 USPQ 1389 (BPAI 1993). Although the reference does not specifically state that the antibodies were produced by the PM-2 cell line having DSMZ Accession No. DSM ACC2600, the claimed product appears to be the same as the prior art product, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA).

Additionally, given that Brändlein et al. is co-authored by the inventors of the instant invention and the PM-2 antibody was produced by the same method as that of the instant

invention and exhibits the same properties as the antibody of the instant invention, the product of the prior art comprises the same product as claimed in the instant invention, that is an antibody that specifically binds to CACO-2 cell line (ATCC Accession No. HBT-37), COLO-320 cell line (DSMZ Accession No. ACC 144), or COLO-206F cell line (DSMZ Accession No. ACC 21), thus the claimed product is anticipated because the product will inherently be an antibody specifically binds to CACO-2 cell line (ATCC Accession No. HBT-37), COLO-320 cell line (DSMZ Accession No. ACC 144), or COLO-206F cell line (DSMZ Accession No. ACC 21). See Ex parte Novitski 26 USPQ 1389 (BPAI 1993). Although the reference does not specifically state that the antibodies specifically bind to CACO-2 cell line (ATCC Accession No. HBT-37), COLO-320 cell line (DSMZ Accession No. ACC 144), or COLO-206F cell line (DSMZ Accession No. ACC 21), the claimed product appears to be the same as the prior art product, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA).

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 111-123 and 126-134 are rejected under 35 U.S.C. 102(b) as being anticipated by Brändlein et al. (Amer. Assoc. Can. Res., 2002, 43:970, abstract #4803, IDS) as evidenced by Brändlein et al. (Human Antibodies, 18 April 2002, 11:107-119, IDS).

The claims are as set for above.

It is noted that the specification teaches that by "purified" or "isolated" is meant separated from other components that naturally accompany it. A substantially pure factor may be obtained by chemical synthesis, separation of the factor from natural sources, or production of the factor in a recombinant host cell that does not naturally produce the factor, see p. 17, lines 20-29. Thus it is assumed for examination purposes that monoclonal antibodies produced by hybridomas in cell culture are purified antibodies.

Brändlein et al. (Human Antibodies, 18 April 2002, 11:107-119, IDS) teach as set forth above.

Brändlein et al. (Amer. Assoc. Can. Res., 2002, 43:970, abstract #4803, IDS) teach the PM-2 antibody produced from hybridomas cells that were generated by fusing the cells from lymph nodes from pancreatic carcinoma patients with heteromyeloma cells. Brändlein et al. (Amer. Assoc. Can. Res., 2002, 43:970, abstract #4803, IDS) teach that PM-2 antibody was specific for malignant tissues and show only limited reactivity with healthy cells.

Given that both Brändlein et al. publications are co-authored by the inventors of the instant invention and the PM-2 antibody was produced by the same method as that of the instant invention and exhibits the same properties as the antibody of the instant invention, the product of the prior art comprises the same product as claimed in the instant invention, that is a purified antibody or functional fragment thereof, wherein said antibody or said functional fragment specifically binds a polypeptide having an approximate molecular weight of 55 or 115 kDa using sodium dodecyl sulfate polyacrylamide gel electrophoresis, and wherein said polypeptide is expressed by ASPC-1 (ATCC Accession No. CRL-1682) and BXPC-3 (ATCC Accession No.

CRL- 1687) cells and wherein said antibody or said functional frazment comprises a sequence at least 80% identical to the sequence of SEQ ID NO: 5 or comprises a sequence at least 80% identical to the sequence of SEQ ID NO: 7, thus the claimed product is anticipated because the product will inherently be purified antibody or functional fragment thereof, wherein said antibody or said functional fragment specifically binds a polypeptide having an approximate molecular weight of 55 or 115 kDa using sodium dodecyl sulfate polyacrylamide gel electrophoresis, and wherein said polypeptide is expressed by ASPC-1 (ATCC Accession No. CRL-1682) and BXPC-3 (ATCC Accession No. CRL- 1687) cells and wherein said antibody or said functional frazment comprises a sequence at least 80% identical to the sequence of SEQ ID NO:5 or comprises a sequence at least 80% identical to the sequence of SEQ ID NO:7. See Ex parte Novitski 26 USPQ 1389 (BPAI 1993). Although the reference does not specifically state that the antibodies comprise SEQ ID NO: 5 and/or 7, the claimed product appears to be the same as the prior art product, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA).

Furthermore, given that both Brändlein et al. publications areco-authored by the inventors of the instant invention and the PM-2 antibody was produced by the same method as that of the instant invention and exhibits the same properties as the antibody of the instant invention, the product of the prior art comprises the same product as claimed in the instant

invention, that is an antibody produced by the PM-2 cell line having DSMZ Accession No. DSM ACC2600, thus the claimed product is anticipated because the product will inherently be an antibody produced by the PM-2 cell line having DSMZ Accession No. DSM ACC2600. See Ex parte Novitski 26 USPQ 1389 (BPAI 1993). Although the reference does not specifically state that the antibodies were produced by the PM-2 cell line having DSMZ Accession No. DSM ACC2600, the claimed product appears to be the same as the prior art product, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA).

Additionally, given that both Brändlein et al. publications are co-authored by the inventors of the instant invention and the PM-2 antibody was produced by the same method as that of the instant invention and exhibits the same properties as the antibody of the instant invention, the product of the prior art comprises the same product as claimed in the instant invention, that is an antibody specifically binds to CACO-2 cell line (ATCC Accession No. HBT-37), COLO-320 cell line (DSMZ Accession No. ACC 144), or COLO-206F cell line (DSMZ Accession No. ACC 21), thus the claimed product is anticipated because the product will inherently be an antibody specifically binds to CACO-2 cell line (ATCC Accession No. HBT-37), COLO-320 cell line (DSMZ Accession No. ACC 144), or COLO-206F cell line (DSMZ Accession No. ACC 21). See Ex parte Novitski 26 USPQ 1389 (BPAI 1993). Although the

reference does not specifically state that the antibodies specifically bind to CACO-2 cell line (ATCC Accession No. HBT-37), COLO-320 cell line (DSMZ Accession No. ACC 144), or COLO-206F cell line (DSMZ Accession No. ACC 21), the claimed product appears to be the same as the prior art product, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA).Thus, Capurro et al. anticipates the claimed invention and th rejection of claims 8-11 and 13-16 under 35 U.S.C. 102 (b) is deemed proper.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 124 and 125 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brändlein et al. (Amer. Assoc. Can. Res., 2002, 43:970, abstract #4803, IDS) as applied to claims 111-123 and 126-134 above, and in further view of Taylor (US Patent No. 5,001,225, December, 8 1986).

The claims are drawn to:

124. The purified antibody or functional fragment thereof of claim 111, wherein said functional fragment is selected from the group consisting of VL, VH, Fv, Fc, Fab, Fab', and $F(ab')_2$.

125. The purified antibody or functional fragment thereof of claim 111, wherein said antibody or said functional fragment is linked or conjugated to a detectable agent.

It is noted that the specification teaches that by "purified" or "isolated" is meant separated from other components that naturally accompany it. A substantially pure factor may be obtained by chemical synthesis, separation of the factor from natural sources, or production of the factor in a recombinant host cell that does not naturally produce the factor, see p. 17, lines 20-29. Thus it is assumed for examination purposes that monoclonal antibodies produced by hybridomas in cell culture are purified antibodies.

Brändlein et al. (Amer. Assoc. Can. Res., 2002, 43:970, abstract #4803, IDS) teach as set forth above.

Taylor teaches that Fab and $F(ab')_2$ fragments lacking the Fc fragment of an antibody, clear more rapidly from circulation and have less nonspecific tissue binding than intact antibody (col 9, lines 22-25) and further teach that Fab, F(ab')2 fragments may be used as well as the intact antibody in methods of detection and treatment (col 9, lines 26-32). Taylor also teaches labeling the antibody of the invention by well known art methods, see Col. 9, lines 33-45.

Thus it would have been *prima facie* obvious it would have been *prima facie* obvious to one of ordinary skill in the art and one would have been motivated with a reasonable expectation of success to use antibody fragments to the claimed antigens for the contemplated treatment of cancer, see Examples 7 and 8 of the instant specification, given the state of the art time the invention was made included the knowledge of how to make such fragments and these fragments afford therapeutic advantages in serum half-life. Additionally, it would have been *prima facie* obvious it would have been *prima facie* obvious to one of ordinary skill in the art and one would have been motivated with a reasonable expectation of success to use labeled antibodies for the

detection of the claimed antigen in cell or tumor samples because labeling of antibodies is conventionally done to detect the antigen is directed.

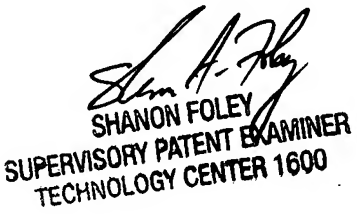
Thus one of ordinary skill in the art would have had motivation and a reasonable expectation of success in making and using the claimed invention.

15. No claims allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter J. Reddig whose telephone number is (571) 272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on (571) 272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Peter J. Reddig
Examiner
Art Unit 1642



PJR